Model Building Process

1. Create healthy adult model in PK Sim – see Compound File and Healthy Adult Individual and Population Files below
2. Scale healthy adult model to children in PK Sim – see Child Individual and Population Files below
3. Export child model to MoBi and add ECMO compartment – see MoBi file
4. In MoBi add Edema Disease State – see MoBi file
    a. Assume XX% increase in total body weight due to edema
    b. Modify fraction interstitial (F_{int}) in Parameter Start Values by assigning the relative increase in weight to the interstitial compartment of each organ
5. Export model back to PK Sim for population simulations
    a. For the Edema model a special Edema Population needs to be created
    b. The edema values will be automatically populated into the population file in PK Sim for all parameters except Fat F_{int}, Muscle F_{int}, and Lung fraction vascular (F_{vasc}). These values either have ontogeny assigned to them (Fat F_{int}, Muscle F_{int}) or have differences based on gender (Lung F_{vasc}). As such, PK Sim will overwrite any MoBi values for these three parameters
    c. To create the Edema Population:
        i. Increase all organ volumes based on XX% edema
        ii. Modify Fat F_{int}, Muscle F_{int}, and Lung F_{vasc} according to step 4 above
    d. In the population file replace alpha-1 acid glycoprotein ontogeny based on Maharaj et al[1] using the following equation:

$$= \frac{Age\ (days)^{0.735}}{11.53^{0.735} + Age\ (days)^{0.735}}$$

    e. In PK Sim change Protein Ratio (interstitial/plasma) from default 0.37 to 1

Reference

1. Maharaj AR, Gonzalez D, Cohen-Wolkowiez M, Hornik CP, Edginton AN. Improving Pediatric Protein Binding Estimates: An Evaluation of alpha1-Acid Glycoprotein Maturation in Healthy and Infected Subjects. *Clin Pharmacokinet.* Aug 4 2017.

Fluconazole Compound File	
Basic Physico-chemistry	
Is small molecule:	Yes
Molecular Weight	306.27 g/mol
Effective Molecular Weight	272.27 g/mol
pKa value	2.56
Compound type	Base
Lipophilicity	1.10
Fraction Unbound	0.89
Solubility	1.00 µg/mL
Solubility Reference pH	7
Solubility gain per charge	1000
Absorption	
Specific Intestinal Permeability	2.22×10^{-6}
Specific Organ Permeability	8.89×10^{-4}
Distribution	
Partition coefficients	Rogers and Rowland
Cellular permeabilities	PK-Sim Standard
Metabolism	
UGT2B7	
Process Type:	Intrinsic clearance – First Order
Volume (liver)	2.36L
Fraction intracellular (liver)	0.67
Intrinsic clearance	8.00×10^{-3} 1/min
Specific clearance	5.09×10^{-3} 1/min
Transport & Excretion	
Renal Clearance	
GFR fraction	0.17

Healthy Adult Individual File	
Biometrics	
Species	Human
Population	European (ICRP, 2002)
Gender	Male
Age	30 y
Weight	73 kg
Height	176 cm
BMI	23.57 kg/m^2
Anatomy and Physiology	
Default values	
Expression	
Metabolizing Enzymes	UGT2B7 (PK Sim Gene Database)
Protein Binding Partners	ORM1 (PK Sim Gene Database)

Healthy Adult Population File	
Demographics	
Number of individuals	1000
Proportion of females	50%
Age Range	18-55 y
Expression	
Metabolizing Enzymes	UGT2B7 (PK Sim Gene Database)
User Defined Variabilty	
Enzymes, Transporters, and Binding Partners	UGT2B7 (Mean 1.00 µmol/l; Geometric Stand Dev 1.34)

Child Individual File	
Biometrics	
Species	Human
Population	White American (NHANES, 1997)
Gender	Male
Age	104 d
Weight	4.6 kg
Height	58.12 cm
BMI	13.62 kg/m^2
Anatomy and Physiology	
Default values	
Expression	
Metabolizing Enzymes	UGT2B7 (PK Sim Gene Database)

Child Population File	
Demographics	
Number of individuals	1000
Proportion of females	50%
Age Range	1-392 d
Expression	
Metabolizing Enzymes	UGT2B7 (PK Sim Gene Database)
User Defined Variabilty	
Enzymes, Transporters, and Binding Partners	UGT2B7 (Mean 1.00 µmol/l; Geometric Stand Dev 1.34)